From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	06.10.2000
Applicant's or agent's file reference: HERY 011	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00003	05/01/2000	06/01/1999

International Patent Classification (IPC) or both national classification and IPC

A61K31/167

Applicant

HENRY, RICHARD

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 06/05/2001.

Name and mailing address of the international preliminary examining authority:
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I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-16 as originally filed

Claims, No.:

1-14 as received on 24/07/2000 with letter of 17/05/2000

Drawings, sheets:

1/3-3/3 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-8,14,

because:

☒ the said international application, or the said claims Nos. 1-8,14 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1,3-8
Inventive step (IS)	Claims	2,9-14
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item I
Basis of the opinion

1. The amendments filed with the letter dated 17th May 2000 introduce subject matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following;

   a) The reference in Claims 1 and 14 to the alkalinizing agent being provided in sufficient quantity to raise the pH of the bladder "*to approximately the pKa of the local anesthetic*"; in this regard, it is noted that the originally filed description indicates (i) that it would in general be desirable that the intra-vesical pH be elevated "*closer to the pKa of the local anesthetic*" (see page 8 lines 17 to 20); (ii) each local anaesthetic has an optimum basic pH for absorption (see page 7 lines 7 to 10) and; (iii) in the case of lidocaine it would seem that the optimum pH range for absorption, i.e. pH 8.0 to 8.3 (see page 14 line 26 to page 15 line 5 and Table 1) is slightly above the pKa for lidocaine (pH 7.9) (see page 9 lines 6 to 15) Nevertheless, there is no disclosure that there is a link between the optimum pH for absorption and the pKa and there seems to be no clear teaching in this document that in every case, *i.e.* under all conditions and with all local anaesthetics, the intra-vesical pH should be raised to approximately the pKa of the local anaesthetic.

   b) the definition in Claim 13 that a "*quantity of alkalinizing agent is 5 to 50 ml of 2-20% sodium bicarbonate*"; in this regard, the originally filed description only appeared to disclose a concentration range of bicarbonate of from "*2-10%*" (see page 12 lines 27 to 29).

   c) the method of Claim 14 that involves *"the steps of periodically administering to a patient..Etc*"; in particular no reference to periodic administration can be found in the originally filed description.

2. Hence, the amendments identified above have not been taken into account when making the following assessment of novelty and inventive step of the claims.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3. Claims 1 to 8 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4. The present application relates to methods for anaesthetizing a patient's bladder using a local anaesthetic in combination with an alkalinizing agent (Claims 1 to 8); pharmaceutical combinations for anaesthetizing a patient's bladder comprising a local anaesthetic and an alkalinizing agent in a syringe (Claims 9 to 13) and methods of treating interstitial cystitis using a local anaesthetic in combination with an alkalinizing agent (Claim 14).

5. Claims 1 to 8 and 14 relate to methods of treatment of the human or animal body by therapy (see present page 1 lines 12 to 17), surgery (see present Claim 3) and diagnosis (see present page 9 lines 16 to 17). In this regard, for the assessment of these claims with respect to industrial applicability, no unified criteria exist in the PCT. Furthermore, patentability can be dependent on the formulation of the claims. The EPO, for example does not recognize as industrially applicable, the subject matter of claims directed to a method of treatment of the human or animal body or to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D4 as follows;

D1: British Journal of Urolology (1979) 51(6) 500-503

D2: British Journal of Urolology (1987) 60(6) 516-518

D3: The Journal of Pharmacology and Experimental Therapeutics (1965) 150(1) 152-159

D4: Scandinavian Journal of Urology and Nephrology (1994) 28 (4) 359-64

D5: *US-A-5137528

D6: *BIOSIS Abstract Accession No 0692950 & Asklin B *et al*, Scand. J. Urol. Nephrol. 23(4), 1989, pp 311-312

* documents D5 and D6 were known to the International Preliminary Examining Authority and copies are enclosed herewith

Claims 1 to 8; methods for anaesthetizing a patient's bladder

7. Document D1 discloses that detrusor instability can be treated by anaesthetising the bladder of the patient. This anaesthetic treatment is performed by introducing 40 ml of 1% lignocaine solution with 40 ml of an 8.4% solution of sodium bicarbonate through a urethral catheter into the bladder (see the "Patients and Methods" on pages 500 to 501 of D1).

8. Document D2 similarly discloses treatment of patients with detrusor instability by filling the bladder with lignocaine hydrochloride in bicarbonate solution (see the "Patients and Methods" on page 516 of D2).

9. Thus, the subject matter of Claims 1 and 3 to 8 is not new in view of the disclosures of each of documents D1 or D2 (Article 33(2) PCT).

10. None of the documents appears to disclose a method according to present Claim 2 wherein the local anaesthetic and alkalinizing agent are provided to the bladder separately.

11. Thus, the subject matter of Claim 2 is new (Article 33(2) PCT).

12. The closest prior art in respect of Claim 2 is considered to be document D1. As indicated herein above, this document discloses treatment of detrusor instability by intra vesical instillation of lignocaine and sodium carbonate. It is further noted that this document indicates that sodium bicarbonate is necessary in order to achieve alkalinization of the bladder contents for the most effective action of the lignocaine solution. (see the "Discussion" on pages 502 to 503 in D1). This document does not, however, clearly disclose if the lignocaine and sodium bicarbonate solution were introduced separately or together.

13. It is considered however that separate administration of the local anaesthetic and alkalinizing agent as set out in Claim 2 is insufficient to confer inventive step on the subject matter of this claim. In this regard, it seems that administration of said local anaesthetic and alkalinizing agent must either be carried out together or separately and that there is no surprising technical effect resulting from either of these alternative modes of administration.

14. Thus, the subject matter of Claim 2 is not inventive in view of the disclosure of document D1 (Article 33(3) PCT).

Claims 9 to 13 combinations for anaesthetizing a patient's bladder

15. For reasons substantially as set out in respect of Claim 2 (see herein above), it is considered that the subject matter of Claims 9 to 13 is new (Article 33(2) PCT) but is not inventive in view of the disclosure of document D1 (Article 33(3) PCT). In this regard, as indicated above it is considered that methods of anaesthetizing the bladder via separate instillation of local anaesthetic and alkalinizing agent into the bladder are obvious. Present Claim 9 merely appears to relate to a conventional single use disposable syringe that has been adapted to carry out the obvious method of Claim 2. This adaptation is considered to be routine and makes no inventive contribution to the present art.

16. In support of the above comments, the Applicant's attention is drawn to the disclosure of document D5 that describes a syringe comprising both a local

anaesthetic and an alkalinizing agent.

Claim 14; methods for treating interstitial cystitis

17. None of the presently cited documents disclose methods of treating interstitial cystitis using a local anaesthetic in combination with an alkalinizing agent. Thus, the subject matter of Claim 14 is new (Article 33(2) PCT).

18. The following comments are however relevant to lack of inventive step of Claim 14; document D6 shows that treatment of interstitial cystitis using a local anaesthetic, *i.e.* lidocaine is known. In view of the teaching in each of documents D1 or D2 that the optimal anaesthetic effect is achieved at an alkaline pH, it is considered obvious to add an alkalinizing agent to the treatment of document D6. In this regard, the improved effects of the new treatment, *i.e.* enhanced anaesthetic effect could have been predicted by one skilled in this art with reference to either of documents D1 or D2.

19. Thus, the subject matter of Claim 14 is not inventive in view of the disclosure of document D1 (Article 33(3) PCT).

Re Item VII
Certain defects in the international application

20. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

2/9/10 (item 10 from file:
DIALOG(R)File 5:Biosis Previews(R)

06929508 BIOSIS NO.: 000089062902
INTRAVESICAL LIDOCAINE IN SEVERE INTERSTITIAL CYSTITIS CASE REPORT
AUTHOR: ASKLIN B; CASSUTO J
AUTHOR ADDRESS: DEP. UROL. AND SURG., CENTRAL HOSP., MOLNDAL, SWEDEN.
JOURNAL: SCAND J UROL NEPHROL 23 (4). 1989. 311-312.
FULL JOURNAL NAME: Scandinavian Journal of Urology and Nephrology
CODEN: SJUNA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We report on a patient with a 2-year history of severe interstitial cystitis with disabling symptoms of painful urgency and urinary incontinence. The condition is characterized by a severe inflammatory reaction in the cystic wall and varying degrees of success for most therapeutic measures employed. Repeated vesical instillations of lidocaine in the urinary bladder relieved the patient from her pain and induced a long-lasting and potent anti-inflammatory effect on the cystic wall. Plasma lidocaine concentrations were below toxic levels and no adverse reactions were reported.